## REMARKS

Claims 1, 2, and 4-15 are pending before the Examiner in the present Office Action of the instant application. Claims 6-15 are withdrawn from consideration. Claim 1 has been amended to include the subject-matter of original claim 4. Claim 4 has been canceled.

Support for the amendments to the claims can be found throughout the specification and claims as originally filed. No new matter has been added as a result of the amendments.

The foregoing amendments have been made solely to claim more fully the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in one or more subsequent applications.

Further, it is respectfully submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as the changes place the application in condition for allowance.

### *A. The rejections under 35 U.S.C. § 112, first paragraph, are overcome*

***Enablement***

The Examiner maintains the previous rejection of claim 4 and now rejects claims 1, 2, and 5 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. In brief, the Action states that Applicant's arguments have been considered but not found persuasive and maintains that "the teaching of the specification cannot be extrapolated to enable the claims because one of skill in the art could not predict that the invention would function as claimed. In particular, the teaching in the specification is not sufficient to establish that a Raf kinase inhibitor would have an affect [sic] on adrenomedullin RNA levels in tumors in

vivo because of the art recognized differences between tumor cells derived from a cell line and tumor cells in an in vivo tumor." See Office Action mailed October 11, 2006, page 4, lines 7-12.

Applicants respectfully disagree with the Office Action and traverse the rejection.

Applicants have specifically limited claim 1 to the single biomarker adrenomedullin, whose expression in tumor-bearing animals treated with a Raf kinase inhibitor has been shown to change (vs. vehicle-treated) (Table 1, Figures 1 and 2).

Cell lines derived from tumors and tissues are commonly used in the laboratory examination of tumor-related phenomena and evaluation of the effectiveness of anti-cancer drugs. This is necessitated by the limited abundance of tissue samples and the understandably stringent guidelines for *in vivo* (both animal and human) preclinical and clinical testing. Evaluation of an anti-cancer therapy in cultured cells is the essentially requisite first step in the treatment's potential eventual evaluation in a relevant animal model or even human being. Indeed, beginning with *in vitro* evaluation is standard operating procedure for the person of ordinary skill in the art. Voskoglou-Nomikos, *et al.* state that "Both basic science studies and clinical trials are essential components of the cancer discovery process." (2003 Clin Cancer Res 9:4227-4239, "Introduction" section)

As to the predictability of a correlation between cultured cells and cancer cells *in vivo* with respect to the efficacy of an anti-cancer therapy, Applicants argue that, despite the variance in degree of predictability afforded by other distinct *in vitro* assays, *in vitro* cell lines do retain clinical predictive value. Voskoglou-Nomikos, *et al.*, after having conducted a literature-based, retrospective study to examine the clinical predictive value of a number of preclinical models, including the *in vitro* human tumor cell line, concluded that "...the *in vitro* cell line model was found to be predictive of Phase II clinical performance for NSCLC under the disease-oriented approach in breast and ovarian cancers under the compound-oriented approach and in case of all four tumor types together." ("Discussion" section).

As regards the Examiner's statement that "Applicant's third argument that Example 1 describes a mouse tumor xenograft model...and that the mouse model data 'correlates' with the claimed invention are not found persuasive...because the example does not teach that the employed kinase inhibitor was effective in the treatment of cancer." Applicants respectfully disagree.

In the first [?], Applicants point out that Example 1 depicts change in expression of adrenomedullin in tumor-bearing animals treated with a Raf kinase inhibitor vs. vehicle-treated (Table 1, Figures 1 and 2). Thus, Example 1 effectively exemplifies the subject-matter of claim 1, which has been specifically limited to the single biomarker adrenomedullin -- that is, the response of a patient being treated for cancer via administration of a Raf kinase inhibitor is monitored through observation of the changing expression of adrenomedullin.

Applicants further respectfully point out that the pending claims are directed to a method of monitoring the response of a patient being treated for cancer, and not to a method of treating cancer. In the Background of the Invention section of the application, it is stated that "...activation of Raf kinase, is considered an important mechanism by which cancer develops.", and that "A number of studies have suggested that inhibition of Raf kinase is an important target for cancer therapy." (page 2, lines 1-4). It is further stated that "Adrenomedullin is a secreted survival or growth factor that has been shown to be secreted by many human tumor types...and human tumor cell lines..." (page 2, lines 28-30). In the present application, adrenomedullin activity in a subject with cancer is measured, and a change in such activity upon administration of a test compound reflects the test compound's usefulness in the treatment of cancer. Claim 1 has been amended to reflect just that – it has been limited to the single marker adrenomedullin.

The Examiner further remarks that "Applicant's fourth argument that enablement is not precluded by the necessity for some experimentation such as routine screening...is not found to be persuasive because, in the instant case, the specification does not provide sufficient guidance to indicate that the invention would predictably function as claimed even with experimentation." Applicants respectfully respond that the mouse model data provided through Example 1 does provide sufficient guidance, in view of the amendment of claim 1 to specify the single biomarker adrenomedullin and in view of the above arguments. As previously stated, *In re Brana* states that such mouse models are "widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound" and thus, are accepted modes of testing compound effectiveness for use in humans. *In re Brana*, 51 F.3d at 1563.

In light of the fact that the claimed methods are diagnostic by nature, and because of the clinical predictive value of the *in vitro* experiments, the guidance for conducting the methods provided by the specification, which includes several examples (even an animal model), is quite extensive. Furthermore, as stated above, claim 1 has been amended to specify that the biomarker

is adrenomedullin, as specifically exemplified in Example 1 and demonstrated in Figures 1 and 2.

Accordingly, it is respectfully submitted that adequate guidance is provided to enable the skilled artisan to practice the claimed invention without undue experimentation. Therefore, reconsideration and withdrawal of the U.S.C. § 112, first paragraph rejections are earnestly solicited.

***Written description***

The Examiner rejects claims 1-2 and 4-5 under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. Specifically, the Examiner asserts that "...the specification does not provide an adequate written description of 'a Raf kinase inhibitor' and therefore, does not provide an adequate written description of the claimed method that employs 'a Raf kinase inhibitor'." The Examiner further asserts that "...the instant specification has not established a correlation between structure and function for any Raf kinase inhibitor and thus a class of Raf kinase inhibitors that would function as claimed in the specification has not been described."

Applicants respectfully disagree with the rejection and traverse as follows.

As mentioned previously, in *Falkner v. Inglis,* 448 F.3d 1357 (Fed. Cir. 2006), the court held the following as being consistent with the current law of written description: "(3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Id.* at 1366. Further, the court in considering whether Inglis' failure to provide any DNA sequences of the poxvirus genome or the locations of the "essential" genetic regions to be deleted should fail the written description requirement, held that no such disclosure was required because the sequences were already known in the art. *Id.* at 1367.

The Examiner states that Applicants' arguments have been considered but not found persuasive, because "...while the art may provide structure for various Raf kinase inhibitors, the instant specification has not established a correlation between structure and function for any Raf kinase inhibitor and thus a class of Raf kinase inhibitors that would function as claimed in the specification has not been described." Furthermore, the Examiner states that "...without the description of at least Raf kinase inhibitor that would function as claimed one of skill in the art could not determine that the inventors were in possession of the claimed invention at the time the

application was filed." Applicants respectfully disagree. Example 1 specifically exemplifies the subject-matter of amended claim 1, namely, the monitoring of response of a subject being treated for cancer via administration of a Raf kinase inhibitor by comparing the levels of expression of the single biomarker adrenomedullin in samples taken from the subject over a course of treatment. Raf kinase inhibitors are well-known and have been well-characterized for the person of ordinary skill in the art (as stated in the previous response, Raf kinase inhibitors have been described in U.S. Patent No. 7,071,216, which also incorporates by reference the Raf kinase inhibitors described in (a) Crump, Current Pharmaceutical Design, 2002, 8:2243-2248, (b) Sebastien et al., Current Pharmaceutical Design, 2002, 8:2249-2253, (c) Kolch et al., Nature, 1991, 349:416-428, (d) Monia et al., Nature Medicine, 1996, 2:668-675, and (e) U.S. Patent Nos. 6,458,813, 6,391,636, 6,358,932, 6,268,391, 6,204,467, 6,037,136 and 5,717,100). Any Raf kinase inhibitor is within the scope of the invention, as long as the effectiveness of employing it in the treatment of cancer in a subject can be monitored by examining the expression level of the biomarker adrenomedullin over a course of the treatment in the subject. There is no reason for the ordinary skilled artisan to expect a significantly different result (for example, no change in the expression of adrenomedullin) for treatment with different Raf kinase inhibitors. Indeed, the fundamental discovery of the invention is not that of a single novel Raf kinase inhibitor; rather, the inventors found a significant link between inhibiting a Raf kinase and an effect on adrenomedullin levels. To effectively monitor the efficacy of treatment of cancer in a subject with Raf kinase inhibitors, the result of import is whether there is inhibition of a Raf kinase, as assessed herein by the measurement of the expression levels of the biomarker adrenomedullin during treatment. Applicants have amended claim 1 to reflect exactly that – amended claim 1 is limited to the single marker adrenomedullin.

Accordingly, Applicants maintain that the presently claimed invention meets the requirements under 35 U.S.C. § 112, first paragraph with respect to written description. Reconsideration and withdrawal of the Section 112 rejections are respectfully requested.

## REQUEST FOR AN INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner (and SPE, if appropriate) are respectfully requested. The Examiner is asked to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

*Inventors: Eveleigh et al.*
*Serial No.: 10/675,406, filed September 30, 2003*

*Attorney Docket No. 5138*
*[66816 (54716)]*

## CONCLUSION

In view of the foregoing amendments and remarks presented herein, reconsideration and withdrawal of all rejections and allowance of the instant application with all pending claims are respectfully solicited.

The Commissioner is authorized to charge any additionally required fee, or credit any overpayment, occasioned by this submission to Deposit Account No. 04-1105.

Respectfully submitted,

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